DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR 1,1,1-TRICHLOROETHANE

Prepared by:

Syracuse Research Corporation
Environmental Science Center
301 Plainfield Road, Suite 350
Syracuse, NY 13212

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service
Cassandra Smith, Work Assignment Manager

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Peer reviewers for the pre-public comment second draft of the Toxicological Profile for 1,1,1-Trichloroethane were:

Bhupendra Kaphalia, Ph.D.
Associate Professor, Department of Pathology
University of Texas Medical Branch
Galveston TX

Kannan Krishnan, Ph.D.
Professor and Director, Human Toxicology Research Group
University of Montreal
Pierrefonds, PQ H9J 3R4, Canada

Gary Stoner, Ph.D.
Professor, Environmental Health Sciences
Ohio State University School of Public Health
Columbus, OH

ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document, "P" indicates a page number in the second draft of the profile, and "L" indicates the line number on that page.

Review comments provided by Dr. Bhupendra Kaphalia:

PR9 (general comment): Dr. Kaphalia suggested numerous editorial changes to the supplemental document.

Response: Most suggested changes were made. However, those that would have required major reorganization of the information provided in description, results, and comments sections were not made due to time constraints.

PR67, P66, L821: Dr. Kaphalia suggested that references be added to the first two paragraphs of Section 3.4.

Response: These paragraphs present a summarizing overview for toxicokinetics. Detailed information with references are contained in the main text of this section. The suggested change was not made.

PR92, P129, L3: Dr. Kaphalia suggested that the extent of transfer via mother's milk is very low.

Response: 1,1,1-Trichloroethane has been detected in mother's milk. It is, therefore, possible for a newborn to be exposed to 1,1,1-trichloroethane via mother's milk. No change was made.

PR92, P129, L18-20; P134, L9-10: Dr Kaphalia suggested that the statement is probably not accurate as children will also exhale due to high alveolar ventilation rate.

Response: Children breathe in more air than adults and therefore, they are exposed to higher volumes of 1,1,1-trichloroethane. The amount of 1,1,1-trichloroethane inhaled may not be equal to the amount exhaled. No changes were made.

All other comments provided by Dr. Kaphalia were addressed as suggested.

Review comments provided by Dr. Kannan Krishnan:

PR20, PA-7: Dr. Krishnan noted that the intermediate-duration oral MRL for 1,1,1-trichloroethane was rounded from 17.7 mg/kg/day to 20 mg/kg/day. Dr. Krishnan indicated that rounding an MRL to the nearest "tens" does not appear to be appropriate.

Response: ATSDR's convention is to round MRLs to one significant figure after all conversions have been made. The intermediate-duration oral MRL for 1,1,1-trichloroethane, therefore, remains rounded to 20 mg/kg/day.

PR20, PA-6: Dr. Krishnan noted that a full uncertainty factor of 10 was used in deriving an intermediate-duration inhalation MRL for 1,1,1-trichloroethane even though a HEC calculation was performed using EPA methodology. Dr Krishnan indicated that a factor of 3 should have been used because the HEC calculation already accounts for the pharmacokinetic component of the uncertainty.

Response: Application of an uncertainty factor of 3 is suggested by EPA and normally applied by ATSDR when dosimetric methodology is applied to extrapolations from animals to humans. ATSDR chose to take a conservative route in the case of 1,1,1-trichloroethane since a blood:air partition coefficient is not available for gerbils and the critical effect in gerbils occurred at an exposure level that was lower than critical effects in other laboratory animals for which blood:air partition coefficients are available. The uncertainty factor of 10 for extrapolation from animals to humans was not reduced to 3.

PR20 (general comment): Dr. Krishnan questioned why results of NTP (1988a, 1988b) studies in rats were not considered in the derivation of an intermediate-duration oral MRL for 1,1,1-trichloroethane.

Response: The NTP (1988a, 1988b) results were not considered because the highest tested doses represented NOAELs and the critical study (NTP 2000) identified a higher NOAEL (1,770 mg/kg/day) that was associated with a LOAEL at the next higher exposure concentration.

PR27 (general comment on references): Dr. Krishnan noted that ATSDR apparently organizes references in the text alphabetically rather than chronologically. Dr. Krishnan asked whether this might be an error.

Response: The convention of ATSDR is to present references alphabetically in the text. It is not an error.

PR30, P90, L1-6: Dr. Krishnan was unclear as to the relevance of the study of Ikatsu and Nakajima (1992) as it relates to the section entitled "Interactions with Other Chemicals."

Response: The point of the discussion of the results of Ikatsu and Nakajima (1992) was to show that some haloalkanes appear to exert a synergistic hepatic effect on animals, particularly in the presence of ethanol, but that 1,1,1-trichloroethane exhibits an apparent protective effect against the hepatotoxicity of haloalkanes such as carbon tetrachloride in the presence or absence of ethanol.

All other comments provided by Dr. Krishnan were addressed as suggested.

Review comments provided by Dr. Gary Stoner:

PR39 (10. Adequacy of the Database), PR277, P96, L10-11: Dr. Stoner expressed concern regarding the proposal for a large number of additional animal and human studies to further evaluate the potential toxic and other effects of 1,1,1-trichloroethane since production of the chemical was supposed to have been terminated in 2002. Dr. Stoner further noted that 1,1,1-trichloroethane does not appear to persist in the environment. He questioned the need to develop a research agenda for 1,1,1-trichloroethane.

Response: Although production was supposed to have been terminated in 2002, a substantial amount of 1,1,1-trichloroethane is still being produced in the United States. Although the chemical is relatively volatile, the degree of current production is cause for continued health concern. ATSDR has identified areas where additional studies have been proposed to fill data gaps. A high priority has not been assigned to the proposed studies; however, information they might provide to a better understanding of 1,1,1-trichloroethane toxicity could be of benefit for purposes of risk assessment.

PR40, PR279, P98, L12-16: Dr. Stoner indicated that proposed oral toxicity studies to assess neurological and cardiovascular effects in animals do not appear to be necessary because there is extensive information on the effects of acute exposure in humans. He further questioned the necessity of proposing acute dermal toxicity animal studies since it is unlikely that accidental or occupational exposure via oral or dermal routes would be of great enough magnitude to cause health concern.

Response: ATSDR has not assigned a high priority to the proposed studies; however, information they might provide to a better understanding of 1,1,1-trichloroethane toxicity could be of benefit for purposes of risk assessment.

PR40, PR281, P100, L1-2: Dr. Stoner stated that available data do not indicate that 1,1,1-trichloroethane should be of carcinogenicity concern. He noted that the compound exhibits only weak mutagenicity and that there is no evidence of promoter activity. He also stated that human exposure is "probably too low to be concerned about carcingenic effects."

Response: ATSDR is of the opinion that the database for 1,1,1-trichloroethane carcinogenicity is weak and that additional animal data, and possibly epidemiological data, could reduce uncertainty regarding the potential carcinogenicity of 1,1,1-trichloroethane.

PR40, PR282, P101, L31-32: Dr. Stoner stated that the proposed immunotoxicity studies do not appear to be warranted since available case reports have not documented marked immunosuppressive effects. He also indicated that such information could probably be obtained from a rather small study.

Response: ATSDR agrees that 1,1,1-trichloroethane does not appear to be of particular immunotoxicity concern. However, the database of information regarding the potential for immunotoxicity is limited and further examination seems warranted.

PR41, PR284, P103, L3-4: Dr. Stoner stated that proposed human dosimetry studies to correlate 1,1,1-trichloroethane levels in human tissues with chronic health effects are highly questionable given the potential toxic effects. He indicated that such studies should be preferably performed using primates.

Response: ATSDR does not intend that experimental dosimetry studies should be performed using human subjects. Rather, tissue and fluid levels of 1,1,1-trichloroethane could be examined in subjects with known exposure to 1,1,1-trichloroethane in an effort to better understand dosimetry issues as they may relate to adverse health effects.

PR213, P14, 26: Dr. Stoner suggested that mention be made of the findings of You et al. (1994), which suggested that reduction in brain cGMP levels may be responsible for the behavioral changes associated with 1,1,1-trichloroethane toxicity.

Response: The authors (You et al. 1994) stated in their report that there appears to be no direct relationship between cGMP levels and neurotoxicity. Therefore, the suggested change was not made.

PR220, P23, L13: Dr. Stoner stated that a disproportionate number of sniffing deaths have occurred in California and New York and that this point could be made.

Response: This information does not appear to be relevant to the purpose of the Toxicological Profile; the suggested information was not added.

PR287, P106, L7-8: Dr. Stoner suggested that the existing database of information regarding potential for age-related differences in susceptibility to 1,1,1-trichloroethane toxicity is probably adequate. The statement indicates that he does not consider additional animal studies of age-related susceptibility to be necessary.

Response: ATSDR is of the opinion that the database of information regarding potential for age-related differences in susceptibility to 1,1,1-trichloroethane toxicity is weak. A single animal study gave some indication of age-related differences in susceptibility, but an additional well-designed animal study seems appropriate.

PR296, P119, L20, L-22: Dr. Stoner circled the subscript x in $NO_{x.}$

Response: The NO_x represents any nitrogen oxide that is present in the atmosphere. No changes were made.

All other comments provided by Dr. Stoner were addressed as suggested.